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SAOUD, CHRISTINE J				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/978,191

Applicant(s)

GODDARD ET AL.

Examiner

Christine J. Saoud

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 December 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 63, 69 and 70 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 63, 69-70 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SF/IC)
- Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Response to Amendment

Claims 63 and 69-70 are pending in the instant application. Claims 1-62 and 64-68 have been canceled in a previous amendment(s).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Applicant's arguments filed 17 December 2007 have been fully considered but they are not deemed to be persuasive.

35 U.S.C. §§ 101 and 112, First Paragraph

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 63 and 69-70 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility, for the reasons of record in the previous Office actions

Claims 63 and 69-70 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth in the instant Office action and for the reasons previously made of record, one skilled in the art clearly would not know how to use the claimed invention.

In the interest of clarity, the basis of the maintained rejections is set forth here:

The claims are directed to isolated polypeptides comprising the amino acid sequence amino acid residues 35-273 of SEQ ID NO: 506. Claims are also presented to chimeric proteins comprising the aforementioned polypeptide. The specification discloses the polypeptide of SEQ ID NO: 506, also known as PRO213-1. Applicants have gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed polypeptides.

At pages 331-345 of the specification, Example 114 discloses a gene amplification assay in which genomic DNA encoding PRO213-1 had a ΔC_t value of at least 1.0 for 34 out of 37 lung tumor samples (and 16 out of 19 lung tumors) and 11 out of 17 colon tumors when compared to a pooled control of blood DNA from several healthy volunteers. Example 114 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the

polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer. ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." It is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at pages 341-345 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.29), and (b) that very few values were obtained that were at least 2.

First, there are several problems with the data provided in this example. The art recognizes that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy **before** the epithelial cells turn cancerous. See Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12), who teach that damaged, precancerous lung epithelium is often aneuploid. See especially p. 4, Figure 4. The gene amplification assay in the instant specification does not provide a comparison between the lung tumor samples and normal lung epithelium and does not correct for aneuploidy. Thus it is not clear that PRO213-1 is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium. One skilled in the art would not conclude that PRO213-1 is a diagnostic probe for lung cancer unless it is clear that PRO213-1 is amplified to a clearly greater extent in true lung tumor tissue relative to non-cancerous lung epithelium.

Second, even if the data had been corrected for aneuploidy and a proper control had been used, the data have no bearing on the utility of the claimed PRO213-1 *polypeptides*. In order for PRO213-1 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO213-1 mRNA or PRO213-1 polypeptide levels in lung or colon tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA levels and polypeptide levels. A specific example of the lack of correlation between genomic DNA amplification and increased mRNA expression is provided by Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

"An analysis of *WISP-1* gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP-3* RNA was seen in the absence of DNA amplification. In contrast, *WISP-2* DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." Another specific example is provided by Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the *abl* gene but to variation in the level of *bcr-abl* mRNA produced from a single Ph1 template" (see abstract).

The *general* concept of gene amplification's lack of correlation with mRNA/protein overexpression in cancer tissue is addressed by Sen (2000, Curr. Opin.

Oncol. 12:82-88). Specifically, Sen teaches that cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Hittelman also speaks to this issue. Again, the data in the specification were not corrected for such aneuploidy events. Furthermore, Godbout et al. (1998, J. Biol. Chem. 273(33):21161-8) speak to general lack of correlation between gene amplification and mRNA/protein overexpression. The abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. ***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified.***" (emphasis added). The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state "***It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell***" (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this

chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO274 confers any growth advantage to a cell, and thus it cannot be presumed that the protein is overexpressed because the genomic DNA including the gene being studied gene is amplified.

An additional reference that provides evidence that gene amplification does not generally lead to increased transcript is Li et al. (2006, *Oncogene*, Vol. 25, pages 2628-2635). Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "***In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels***, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma*." Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that ***it is more likely than not that gene amplification does NOT correlate with increased protein levels***, absent evidence that the protein has biological relevance in cancer. There is no such evidence for PRO341.

Therefore, data pertaining to PRO213-1 genomic DNA do not indicate anything significant regarding the claimed PRO213-1 polypeptides. The data do not support the specification's assertion that PRO213-1 polypeptides can be used as a cancer diagnostic agent. Significant further research would have been required of the skilled artisan to reasonably confirm that the claimed PRO213-1 polypeptides are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO213-1 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO213-1 **polypeptides** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In view of the preponderance of evidence supporting the rejections (Pennica et al., Konopka et al., Sen, Hittelman, Godbout et al., and Li et al., all of which are of record and have been previously discussed), the rejections are properly maintained.

Response to Arguments

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons.

Beginning at page 2-3 of the response, Applicant reviews Example 114 and the data in Table 9, and asserts that an amplification of at least 2-fold is significant and indicative of a cancer diagnostic marker. However, the issue is whether or not a 2 fold amplification of the gene encoding PRO213-1 lung and colon tumor samples is significant. In the instant case, the control used was not a matched non-tumor lung or colon sample but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al., Konopka et al.). This art, as well as the Sen, Hittelman, Godbout et al., and Li et al. references cited above, constitute strong opposing evidence as to whether or not the claimed polypeptides have utility and enablement based on a presumption of overexpression in view of gene amplification data. Finally, this argument does not speak to whether or not the *encoded proteins* are also found at increased levels in cancerous tissues. Since the claims under examination are directed to polypeptides, not genes, this question is critical.

Beginning at page 3 of the response, Applicant refers to the Goddard declaration as establishing that an amplification of at least 2-fold is significant and indicative of a cancer diagnostic marker. The Goddard declaration under 37 CFR 1.132 filed 14 November 2004 is insufficient to overcome the rejection of the claims based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the previous Office actions for the following reasons. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be

established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2-fold amplification of the gene encoding PRO213-1 in lung and colon tumors is significant. The significance can be questioned based on the absence of factual support for the expert's opinion. In the instant case, the fact is that the control used was not a matched non-tumor lung and colon sample but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al., Konopka et al.). This art, as well as the Sen, Hittelman, Godbout et al., and Li et al. references (cited previously), constitute strong opposing evidence as to whether or not the claimed polypeptides have utility and enablement based on a presumption of overexpression in view of gene amplification data. Finally, while the Goddard declaration speaks to the utility and enablement of genes, it does not speak to whether or not the encoded proteins are also found at increased levels in cancerous tissues.

Applicant argues that the articles of Orntoft. et al., Hyman et al. and Pollack et al. teach that in general, gene amplification increases mRNA expression. Applicant further argues that over a hundred references, along with Declarations have been submitted that in general, there is a correlation between mRNA levels and polypeptide levels.

This has been fully considered but is not found to be persuasive. Orntoft et al.

(Molecular and Cellular Proteomics 1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused *abundant* proteins.” (See abstract.) It would appear that Applicant has provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Hyman (Cancer Research 62:6240-6245) found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner asserts that 2% does not provide a reasonable expectation that the slight amplification of PRO213-1 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung or colon cancer.

Applicant also refers to the declaration of Dr. Polakis, submitted under 37 C.F.R. § 1.132 with the response filed July 7, 2006. Applicant previously characterized the declaration as setting forth Dr. Polakis' experience with microarray analysis wherein approximately 200 gene transcripts present in human tumor cells were found to be at significantly higher levels than in corresponding normal human cells. The declaration

goes on to state that antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels compared. The declaration states that in approximately 80% of the cases, the researchers found that increased levels of RNA correlated with changes in the level of protein. Applicant previously concluded that all of the submitted evidence supports Applicant's position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the Examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO213-1 (i.e., data regarding amplification of PRO213-1 genomic DNA), and does not disclose any information regarding PRO213-1 mRNA levels. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al., Konopka et al., Hu et al. (who reviewed 2286 genes

reported in the literature to be associates with breast cancer), Haynes et al., Lian et al., and Fessler et al. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so that the examiner could not independently evaluate them. For example, how many of the tumors were lung tumors? How highly amplified were the genes that correlated with increased polypeptide levels?

Applicant also refers to a Declaration by Dr. Scott, however, this Declaration under 37 CFR 1.132 is insufficient to overcome the rejection of the claims based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action(s) because the declaration focuses on the question of whether or not mRNA levels are predictive of protein levels. Since the Scott declaration does not address the question of whether or not amplified genomic DNA is predictive of increased polypeptide levels, it is not considered pertinent to the rejection.

Applicant asserts at page 5 of the response that a *prima facie* case of lack of utility has not been established. Applicant asserts that it is not legally required that there be a necessary correlation between the data presented and the claimed subject matter. Applicant further argues that the evidentiary standard is a preponderance of the totality of the evidence under consideration. Applicant concludes that the question is whether it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation between gene copy number and protein expression levels.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's assessment of the question to be asked is on point and correct. However, a review of the totality of the evidence under consideration must result in the conclusion that one skilled in the art would reasonably doubt the existence of a positive correlation between protein expression and gene copy number.

Applicant argues that Pennica et al. showed a correlation between DNA amplification and overexpression for WISP-1 and that a change in mRNA without a change in DNA copy number is not contrary to Applicant's assertions. Applicant argues that the fact that the single WISP-2 gene did not show the expected correlation of gene amplification with the level of mRNA/protein expression does not establish that it is more likely than not, in general, that such correlation does not exist. Applicant asserts that the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level, as was demonstrated for WISP-1.

Applicant's argument has been fully considered, but is not persuasive. Alleging that the working hypothesis among those skilled in the art without supporting evidence is an assertion, not a fact. The evidence of record demonstrates that there is not a predictable correlation between DNA amplification and overexpression - Pennica et al. is a reference which clearly demonstrates the difficulties and lack of correlation especially in cancer tissues. Therefore, data pertaining to PRO213-1 DNA do not necessarily indicate anything significant regarding the claimed PRO213-1 polypeptides and the data do not support the assertion that PRO213-1 can be used as a cancer diagnostic.

Applicant argues at pages 6-7 of the response that Pennica et al. is specific to WISP genes and that Pennica et al. and Konopka et al. have no teaching whatsoever about the correlation of gene amplification and protein expression in general. This has been fully considered, but is not found to be persuasive. The instant application also presents data from a single gene at a time and makes conclusions about gene products from genomic DNA data. Pennica and Konopka constitute evidence that it cannot be assumed that amplified genomic DNA results in overexpressed gene product. Godbout et al. and Li et al. also provide evidence to this effect. Finally, Sen, and Hittelman constitute evidence that, in general, non-cancerous epithelial tissues are frequently aneuploid, and thus an increase in genomic DNA is not diagnostic of cancer.

Applicant argues at page 7 of the response that Li et al. does not support the rejection since Li et al. acknowledge that their results differed from Hyman et al. and Pollack et al., and may be due to differences in methodology. Applicant points to supplemental information accompanying the Li et al. publication indicating that genes amplified at a 1.4 copy number were considered significant, whereas PRO213-1 was amplified at least 2-fold. This has been fully considered but is not found to be persuasive. First, it is noted that Hyman et al. also found that less than half of the amplified genes were overexpressed at the mRNA level, even though they only investigated genes in genomic DNA regions that were amplified at least 2-fold (argued in more detail above). Furthermore, Li et al. did not limit their studies to genes that were amplified at less than 2-fold. In fact, the supplemental information indicates that some of the samples were required to bind with a probe requiring at least 2-fold amplification:

Genes with copy number ratio > 1.40 (representing the upper 5% of the CGH ratios across all experiments) were considered to be overrepresented. A genomic fragment that contained six or more adjacent probes showing a copy number ratio > 1.40, or a region with at least three adjacent probes with a copy number ratio > 1.40 **and no less than one probe with a ratio > 2.0**, were considered to be amplicons. (emphasis added, from 1st page of supplemental material)

At pages 8-9, Applicant addresses the Godbout et al. reference. Specifically, Applicant argues that Godbout et al. teaches that there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied, and that this demonstrates that in these cell lines, DDX1 mRNA and protein levels are correlated. Applicant's arguments have been fully considered but are not found to be persuasive. Far from teaching predictability for expression of PRO213-1 on the basis of a minor genomic amplification, the abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state "*It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell* (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both

genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons."

Applicant asserts that they never claimed that PRO213-1 was similar to DDX1 gene of Godbout et al. or that PRO213-1 was an RNA helicase. Applicant contends that the Godbout reference was submitted to show good correlation between protein levels based upon genomic DNA amplification. Applicant's argument has been fully considered, but is not found persuasive. Godbout does not generalize that genomic DNA amplification shows a good correlation between protein levels, but rather, "co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell". As pointed out, this has not been demonstrated with PRO213-1, so there is no expectation that the protein will be overexpressed, absent evidence to the contrary.

Applicant argues that the examiner is focusing on the mechanism by which PRO213-1 acts rather than on the positive result itself. Applicant's argument has been fully considered, but is not persuasive. The Examiner in no way required a mechanism of action or knowledge of a mechanism of action. Applicant is making the assertion that genomic DNA amplification correlates with protein overexpression and cited Godbout to

support this conclusion. However, Godbout states very clearly that *"It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell"* – Godbout does not state that genomic DNA amplification correlates with protein overexpression in general. If Applicant had shown evidence that PRO213-1 was involved in selective growth advantage to the cell, this might be a basis to assert that one would expect the protein to be overexpressed based on the fact that the genomic DNA was amplified. The examiner is not requiring a mechanism be present or disclosed before a protein is allowable, but rather there be a specific and substantial utility for the protein. Based on the genomic DNA levels of PRO213-1, there is no specific and substantial utility for the encoded protein because there is no reasonable expectation that the protein will be overexpressed and therefore, useful for the diagnosis or detection of lung cancer, absent evidence to the contrary.

At pages 10-11, Applicant urges that, in general, DNA amplification correlates with increased expression of the encoded protein. Applicant argues that the specification shows amplification of PRO213-1 in lung primary tumor and colon tumor, evidence in the form of publications has been submitted to establish that a general DNA/mRNA/protein correlation exists, and declarations from experts have been provided to further support Applicant's position. Applicant concludes that the utility of the claimed PRO213-1 polypeptides has been achieved. Applicant stresses that absolute certainty is not required, and that it has been established that it is more likely than not that PRO213-1 polypeptides are overexpressed in certain carcinomas.

This has been fully considered but is not found to be persuasive for the following reasons. The assay did not correct for aneuploidy, which is a common feature of non-cancerous, damaged lung epithelium (evidenced by Hittelman). Contrary to Applicant's assertion, the state of the art indicates that gene amplification is not generally associated with overexpression of the encoded gene product, as evidenced by Sen, Pennica et al., Konopka et al., Godbout et al., Hyman et al., and Li et al. Since significant further research would have been required of the skilled artisan to reasonably confirm that the claimed PRO213-1 polypeptides are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents, the asserted utility is not substantial. In the absence of information regarding whether or not PRO213-1 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO213-1 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on Monday-Friday, 6AM-2PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine J Saoud/
Primary Examiner, Art Unit 1647